ENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference P427472DJJ	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/NZ00/00093**	International Filing Date *(day/month/year)* 9 June 2000	Priority Date *(day/month/year)* 11 June 1999

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] A61D 7/00, A61M 31/00

Applicant

DEC RESEARCH et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
6 December 2000	13 March 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **COLIN FITZGIBBON** Telephone No. (02) 6283 2226

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/NZ00/00093

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: **4, 5, 23 and 30**

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. **4, 5, 23 and 30**

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**7, 9, 16, 19, 20, 22, 29**	**YES**
	Claims	**1-3, 6, 8, 10-15, 17, 18, 21, 24-28**	**NO**
Inventive step (IS)	Claims	**7, 16, 20, 22, 29**	**YES**
	Claims	**1-3, 6, 8-15, 17-19, 21, 24-28**	**NO**
Industrial applicability (IA)	Claims	**1 to 30**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

Novelty (N) Claims 1-3, 6, 8, 10-15, 17, 18, 21, 24-28

D1 WO 98/33452 (DEC INTERNATIONAL NZ LTD)

D2 US 5242565 (WINSEL)

D3 WO 99/07346 (CERAMATEC, INC)

D4 WO 94/01165 (ELAN MEDICAL TECHNOLOGIES LTD)

D5 WO 96/29025 (ADVANCED ANIMAL TECHNOLOGY LIMITED)

The invention defined in each of Claims 1, 3, 6, 8, 10 to 14, 21 and 24 to 28 lacks novelty in light of D1. The citation discloses a body cavity substance delivery device including a battery powered electrical circuit disposed within the housing of the device capable of being energised to generate a gas so as to apply pressure and subsequent movement of a piston within the device and thus cause expulsion of a liquid substance from the device into the surrounding environment.

Similarly, the invention defined in each of Claims 1 to 3, 6, 8, 10 and 18 lacks novelty when compared with D2 and the invention defined in each of Claims 1, 3, 6, 10, 15, 17, 26 and 27 lacks novelty when compared with D3.

Inventive Step (IS) Claims 1-3, 6, 8, 10-15, 17, 18, 21, 24-28

The invention defined in each of Claims 1 to 3, 6, 8, 10 to 15, 17, 18, 21 and 24 to 28 lack an inventive step as per novelty above.

In addition, the invention defined in each of Claims 9, 15 and 17 to 19 lack an inventive step when compared with D1. It is considered that the addition of each of intra-ruminal positioning, water, ethanol and/or benzyl alcohol inclusion in the liquid, and a removable, rupturable or dissolvable cap as defined in each of these claims is an obvious variation to the invention defined in D1, particularly when read in light of D4. Furthermore, the inclusion of a switch capable of being actuated to immediately or after a delay commence the generation of a gas or gases, is merely a technical variation of the invention of D1. The invention defined in Claim 9 is considered to be obvious when read in the light of D5.

Yet further, the invention defined in each of Claims 14, 17, 19 and 21 is considered to be an obvious variation of the invention defined in D2..

Cont'd

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The claims do not comply with Rule 6.2(b) because reference signs in parentheses relating the technical features mentioned to the drawings should be inserted in the claims to increase their intelligibility. This applies to both the preamble and the characterising portions.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Irrespective of the non-establishment of an opinion in regard to Claim 5, it is noted that US 5352464 as referred to in Claim 5 and in the specification, defines a seasoning powder and as such, is in no way related to the present application.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V Reasoned Statement

Inventive Step (IS) Cont'd

The invention defined in each of Claims 8, 11 to 14, 19, 21 and 28 is also considered to be an obvious variation of D3, and the invention defined in Claim 18 is again considered to be a technical variation of the invention defined in D3.

In addition, the invention defined in each of Claims 1, 3, 6, 10, 18, 19 and 26 is considered to be an obvious variation of the invention defined in D4.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published:
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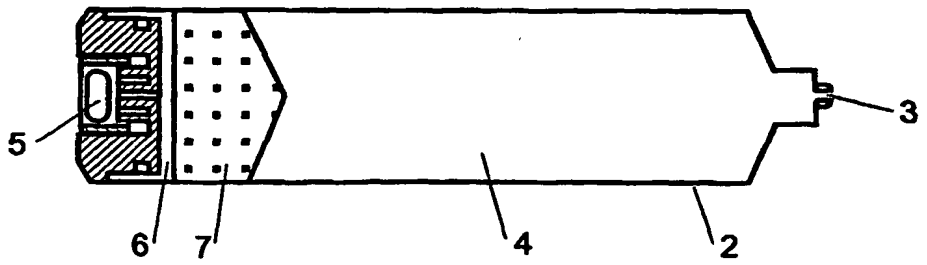
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DEVICE FOR DELIVERY OF A LIQUID VEHICLE



(57) Abstract: An intra vaginal delivery device for a target species mammal comprising or including: an elongate housing defining a barrel with an outlet at one end (the "outlet end"); a piston disposed in said barrel and moveable towards the outlet end to reduce the available volume for liquid between said piston and said outlet; a progesterone including liquid within said barrel between said outlet and said piston, the volume of such liquid preferably being from 5 to 100 mL; wings dependent from said housing capable of self depployment from a vaginal tract insertion condition to assume a vaginal tract retention geometry for the target species mammal; a battery powered electrical circuit disposed in said housing at the non outlet end region thereof capable of being initialised in order to energise the electrical circuit from the battery thereof, such battery (or an electrolytic cell forming part of the circuit) generating, once the electrical circuit is energised, at least one gas confined within said housing, such gas being capable when in sufficient quantities to move said piston along said barrel thereby to express said liquid out through said outlet.

WO 00/76421 A1

DEVICE FOR DELIVERY OF A LIQUID VEHICLE

THE CURRENT INVENTION

The present invention relates to improvements in the delivery of an active agent into an environment (whether *in vivo* or *in vitro*) and particularly, although not solely, to devices having application in the delivery of one or more active ingredients into a mammal (eg; intra ruminally or intra vaginally) or into an aqueous environment, e.g. an aquarium.

SUMMARY OF THE INVENTION

In our PCT/NZ98/00011 we disclose in some detail the background to the passive and active release of active ingredient(s) into the body cavity of mammals including the vaginal tract and the rumen. PCT/NZ96/00024 (WO 96/29025) discloses a microprocessor controlled active release device for intra vaginal insertion with its retention being dependent on variable geometries possible using deployment members of a kind as disclosed in NZ Patent Specifications 193976 and 200564.

A problem discussed in such specification is the release profile of a substance delivery device whether for a body cavity or otherwise (for example, a liquid body such as an aquarium) arising from a passive leakage of material which can affect the overall release profile.

We have investigated different known procedures of active release and have considered new procedures insofar as the means of expression of a liquid vehicle from a reservoir of reducible volume is concerned. It is to such substance delivery devices and their use that the present invention is directed.

In a first aspect the present invention consists in **a (preferably body cavity) liquid delivery device** comprising or including

a housing defining a barrel with an outlet,

a piston disposed in said barrel and moveable to reduce the available volume for liquid between said piston and said outlet,

a liquid within said barrel between said outlet and said piston, and

a battery powered electrical circuit disposed in said housing capable of being

energised to generate gas or gases confined within said housing yet capable of moving said piston along said barrel thereby to express liquid out through said outlet.

Preferably the battery itself of said electrical circuit emits said gas or gases upon energisation of the electrical circuit by said battery.

In another form said electrical circuit defines an electrolysis cell with a hydrogel or electrolyte and the gas issues or gases issue from said hydrogel or electrolyte.

Preferably the battery powered electrical circuit includes a battery of a kind as disclosed in US Patent 5,242,565.

Preferably said battery powered electrical circuit, where an electrolysis cell is involved, includes an electrolysis cell of a kind as disclosed in US Patent 5,352,464.

Preferably said electrical circuit provides a continuous rate of gas production by the action of a continuous current to the electrolysis cell or gas emitting battery.

Alternatively said electrical circuit provides a discontinuous rate of gas production by the action of a discontinuous current, for example, as might be provided by a microprocessor, to the electrolysis cell or gas emitting battery.

Preferably where said battery powered electrical circuit provides a continuous rate of gas production, such production is dependent upon at least one of the group consisting of

(a) a selected resistor in series,

(b) a selected variable resistor and a setting of a desired resistance in series, and

(c) a selected microprocessor to control the current.

Preferably the battery powered electrical circuit is one having a known or calibrated profile of gas generation that will lead to a related profile of liquid release from said outlet.

Preferably said device is an intra vaginal device .

Preferably said housing has associated therewith at least one deployable retention member to enable the retention of the device in the vagina after insertion in the vagina of a target mammal whilst said at least one retention member is not deployed.

Preferably said at least one retention member comprises at least two wings which resiliently deploy once inserted and preferably are no longer restrained by an insertion

tool.

Preferably the retention feature(s) is (are) those typified in the disclosure of PCT/NZ97/00052, PCT/NZ98/00011 and PCT/NZ98/00024 (and any specification referred to therein), the full content of which is hereby here incorporated by way of reference.

Preferably said liquid includes progesterone in an appropriate liquid carrier.

In another embodiment said device is an intra ruminal device.

Preferably said intra ruminal device is retainable in the rumen of a target mammal by means of its density (at least up until the depletion of the liquid from said housing) or by deployment of at least one retention member.

Preferably said liquid includes at least one or more of water, ethanol and benzyl alcohol.

Preferably said battery powered electrical circuit includes a switch capable of being actuated immediately or after a delay to commence the generation of a gas or gases.

Preferably said outlet is provided with a closure capable of being removed or ruptured or dissolved in body fluids.

Preferably said closure is capable of being removed or ruptured under the pressurisation of the liquid within said housing upon energisation of the battery powered electrical circuit.

Preferably said liquid is of a volume of from 5 to 100 mL and said piston is movable within said housing to express substantially all of such liquid from the housing.

Preferably said device is insertable, retainable and removal from the vaginal tract of a target species mammal, there being a conduit or passageway disposed to allow pressure equalisation outside of the device at the innermost and outmost extent of the device in the vaginal tract.

Preferably said device is substantially as hereinafter described with reference to the accompanying drawings.

In still another aspect the invention consists in **an intra vaginal delivery device** comprising or including

a housing defining a barrel with an outlet,

variable geometry vaginal retention means carried by said housing,

a piston disposed in said barrel and moveable to reduce the available volume for liquid between said piston and said outlet,

a progesterone carrying liquid within said barrel between said outlet and said piston, and

a battery powered electrical circuit disposed in said housing capable of being energised to generate gas or gases from the battery of said battery powered electrical circuit, such generated gas or gases being confined within said housing and being capable of moving said piston along said barrel thereby to express liquid out through said outlet

and wherein said battery powered electrical circuit provides a discontinuous or continuous gas production upon initiation of energisation with rate and/or timing dependent upon at least one of the group consisting of

(a) a selected resistor in series,

(b) a selected variable resistor and a setting of a desired resistance in series, and

(c) a selected microprocessor to control the current.

In still a further aspect the present invention consists in **an intra vaginal delivery device** comprising or including

an elongate housing defining a barrel with an outlet at one end (the "outlet end"),

a piston disposed in said barrel and moveable towards the outlet end to reduce the available volume for liquid between said piston and said outlet,

a progesterone including liquid within said barrel between said outlet and said piston, the volume of such liquid being from 5 to 100 mL,

wings dependent from said housing capable of self deployment from a vaginal tract insertion condition to assume a vaginal tract retention geometry for the target species mammal,

a battery powered electrical circuit disposed in said housing at the non outlet end region thereof capable of being initialised in order to energise the electrical circuit from the battery thereof, such battery generating once the electrical circuit is energised at least one gas confined within said housing, such gas being capable when in sufficient

quantities to move said piston along said barrel thereby to express said liquid out through said outlet.

In another aspect the invention consists in **a method of providing an active release of a liquid within a body cavity of a target species mammal** which comprises or includes locating in such a body cavity a device as claimed in any one of the preceding claims with said battery powered electrical circuit energised or committed to be energised.

In still another aspect the invention consists in **a method of delivering an active amount of a progesterone into the vaginal tract of a target species mammal** which comprises

locating a device of the present invention in such tract after initiation of the device, and

allowing the device to actively express the liquid from said housing under the effect, via said piston, of the gas or gases generated by the energised battery powered electrical circuit.

Preferably said method involves removing said device after a sufficient time of liquid delivery.

In another aspect the invention is a method when performed substantially as herein described with or without reference to any one or more of the accompanying drawings.

In still other aspects the present invention consists in a method of providing a delayed release of a liquid vehicle into a body cavity of a mammal or into a liquid environment or other environment which comprises the operative use of a delivery device in accordance with the present invention.

Preferably said devices do not include a dip tube or the equivalent of a kind as defined in, for example, PCT/NZ98/00011.

In still a further aspect the present invention consists in an intra ruminal device which is also a delivery device in accordance with the present invention.

In still a further aspect the present invention consists in an intra vaginal device which is also a delivery device in accordance with the present invention.

In still a further aspect the present invention consists in any of the devices or

apparatus previously defined whereby means is provided to enable for equalisation of pressures between the zone externally adjacent said outlet with some region of the device having a closer access to ambient condition when the device is retained in a body cavity, such means providing for fluid (preferably gas and preferably air) communication to minimise pressure differentials adjacent the outlet as a result of movement of walls of the body cavity and an air seal about the device in the body cavity.

Preferably the arrangement is of any kind typified by the diagrammatic form shown in, for example, Figure 5.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which;

Figure 1A shows a balloon or membrane containing embodiment of a device,

Figure 1B is a piston including syringe-like embodiment,

Figure 2 is a plot for the Figure 1A and B embodiments of volume released against time,

Figure 3 compares for the Figures 1A device the *in vivo* and *in vitro* delivery profiles with a plot of volume release against time,

Figure 4 is a similar comparison for the Figure 1B device plotted in a similar fashion to that of Figure 3,

Figure 5 shows how (in this case for the more energy demanding but better *in vivo* delivery profile device - that of Figure 1B) the use of a tube whereby the transient pressure differentials (eg; in the vaginal tract) adjacent the outlet may be reduced,

Figure 6 is a plot of the plasma progesterone following intra vaginal insertion of a device of Figure 1A,

Figure 7 is a plot of the plasma progesterone following intra vaginal insertion of a device of Figure 1B with three different progesterone formulations,

Figures 8A through 8D show a simple circuit diagram each involving an electrolytic cell, **Figure 8A** shows an electrolytic cell in series with resistor and power source, **Figure 8B** shows an electrolytic cell in series with a variable resistor and power

source, **Figure 8C** shows an electrolytic cell controlled by powered microprocessor and **Figure 8D** shows an electrolytic cell controlled by powered microprocessor,

Figure 9A through 9D show a series of different circuits appropriate where a battery of a kind capable of generating a gas or gases is utilised in the circuit, **Figure 9A** showing a gas cell of the type described by US Patent 5,242,565 in series with a resistor, **Figure 9B** shows a gas cell of the type described by US Patent 5,242,565 in series with a variable resistor, **Figure 9C** shows a gas cell of the type described by US Patent 5,242,565 controlled by a gas cell of the type described by US Patent 5,242,565 powered microprocessor and **Figure 9D** shows a gas cell of the type described by US Patent 5,242,565 controlled by a microprocessor powered by an external power source, and

Figure 10A shows in broken outline two insertion conditions for self deployable wings and **Figure 10B** shows such wings deployed to a vaginal tract retention condition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention recognises advantages that might flow to particularly body cavity retainable devices (eg; intra vaginal or intra ruminal devices) where a liquid vehicle is to be actively released and there is a desire to reduce the ratio of passive release to active release. In this respect embodiments to be discussed hereinafter recognise advantages that arise from the use of gas generation for the purposes of reducing the available volume in a reservoir for the liquid vehicle to be expressed.

For low energy usage preferably an inflatable device as hereinafter described by reference to Figure 1 is preferred yet surprisingly as will hereinafter be described we have determined that a plunger or piston like reservoir reduction provides a better *in vivo* release profile over that of the inflation option owing to a reduction in passive delivery. Where therefore rapid release with some passive content is not of concern significant energy savings are available for an active release device utilising the inflation option. Where however controlled release is of primary importance and/or there is no concern with an initial startup delay or a startup delay is desired the option hereinafter described by reference to Figure 1B with the use of a gas generated battery

is to be preferred even though it will be a higher energy requirement for such an option.

The devices of Figures 1A and 1B utilize electronically controlled gas to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US5352464) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The device of Figure 1A incorporates a balloon that upon the production of gas and its movement into the balloon means the balloon expands to fill the reservoir containing the liquid vehicle. This expansion results in the delivery of the liquid vehicle out of the outlet.

The device of Figure 1B incorporates a piston that upon the production of gas behind the piston results in its migration towards the outlet. This forward migration results in the delivery of the liquid vehicle.

In Figure 1A the balloon 1 is disposed within a syringe like reservoir 2 having an outlet 3. The liquid vehicle 4 is interposed between the walls of the reservoir 2 the outlet 3 and the balloon 1 so that inflation thereof will have the effect of expressing the liquid vehicle 4 out of the outlet 3. The inflation is by means of electronic gas production at 5 which feeds gas via an appropriate conduit 6 to the confines of the balloon or diaphragm 1. Such conduit is indicated as 6.

The arrangement as in Figure 1B is much the same save that instead of the balloon or membrane 1, a piston 7 is provided which will move to reduce the volume for the liquid vehicle 4 therebetween and the outlet 3.

In use when both devices of Figures 1A and 1B are operated with the same rate of gas production the arrangement as shown in Figure 1A with the inflatable balloon allows for a more rapid onset of delivery with a greater flow of vehicle compared to the piston arrangement which is characterised by a lag in the onset of delivery and a reduced delivery rate.

Accordingly for some applications the device of Figure 1 offers advantages over a device of Figure 1B. In the plot of Figure 2, the lag in the onset of delivery from the configuration of Figure 1B is readily apparent from the lower line on the graph,

Preferably the control circuitry involves a resistor (variable or otherwise) of an appropriate kind to affect the current flow. The circuitry may optionally be

microprocessor controlled.

The liquid vehicle is preferably at least primarily aqueous, organic or non-organic as far as its liquid content is concerned. Whilst in preferred forms the vehicle as a whole may be viewed overall as a liquid it need not necessarily be a solution. The liquid itself may be the active or merely a liquid carrier for the active elsewhere in the vehicle.

Accordingly, the term "liquid vehicle" or "liquid" should be interpreted as including any one or more of a suspension, a dispersion, an emulsion, a susproemulsion, a solution and the like, and preferably a progesterone including "liquid".

Whilst the arrangement of Figure 1A has definite efficiencies in respect of the energisation required for the purpose of gas generation per volume of liquid vehicle dispensed and the lack of delay in such dispensation, the device of a kind shown in Figure 1B has been found to improve the delivery of liquid vehicle whilst inserted into a body cavity such as the rumen or the vaginal cavity.

Figure 3 shows a plot of liquid vehicle delivered in grams against time and days with a device as depicted in Figure 1A. The straighter line is the *in vitro* delivery of vehicle from a device of Figure 1A whilst the more curved line represents the *in vivo* delivery profile for an identical device. It is therefore surprising that whilst a device as shown in Figure 1A has the comparative *in vitro/in vivo* profiles shown in Figure 3, that a device as shown in Figure 1B has more agreement between the *in vitro/in vivo* profiles. In this respect see Figure 4 where in a similar way to that of Figure 3 the comparative performance of a device as in Figure 1B is shown in the *in vitro* and *in vivo* delivery modes. That line indicated with the shaded squares represents the *in vivo* profile.

For the purpose of the generation of the data shown in Figures 3 and 4 the volume of liquid vehicle being dispensed was in each case water to be expressed out of a 2 mm diameter outlet. In each case the syringe like reservoir was of a cylindrical form and was powered over the duration of the comparative trials by a galvanic cell of the kind disclosed in US Patent 5242565 capable of generating over the life of the cell to depletion up to 180 ml of hydrogen when measured at normal atmospheric conditions at sea level.

Figure 5 shows a variation of the device as shown in Figure 1A. In this form means is provided to reduce variations at least over the medium term in the pressure differential in a body cavity with that of the ambient atmosphere. For this purpose a tube 8 is provided which, in the case of an intra vaginal device as shown in Figure 5 (the variable geometry wings not being shown for convenience, but do see our PCT/NZ97/00052 (published as WO97/40776)) tends to equilibralise pressure externally of the device in a vaginal tract. Indeed the tube 8 if flexible may serve in part as a withdrawal mechanism for the device and as a passageway 9 through to an outlet zone 10. Experimentation with, for example, cattle has shown in the short to medium terms significant fluctuations in the pressure about the outlet of devices of the kind shown in Figures 1A and 1B which have the effect of providing a different net force acting on the liquid vehicle yet to be expressed. This is particularly disadvantageous with the device of Figure 1A where there is (as demonstrated in Figure 2) a more rapid onset of delivery following any adjustment in pressure on the liquid vehicle.

Accordingly, the device of Figure 1B has a better profile under variations of vaginal tract pressure without any arrangement that seeks to reduce localised pressure variations externally of the device.

Description of the technology:

The devices depicted in Figures 1A and 1B utilize electronically controlled gas **5** to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US 5354264) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The top device of Figure 1A incorporates a balloon that upon the production of gas within **6** the balloon **1** expands to fill the reservoir **2** containing a vehicle **4**. This expansion results in the delivery of the liquid vehicle out of the outlet **3**.

The bottom device of Figure 1B incorporates a piston **7** that upon the production of gas behind **6** the piston results in its migration towards the outlet. This forward migration results in the delivery of vehicle.

Figure 3 shows both the in vitro and in vivo delivery of vehicle from a body cavity for the device of Figure 1A.

Figure 4 shows the in vitro and in vivo agreement of vehicle delivered for the device of Figure 1B.

The device of Figure 5 utilizes electronically controlled gas to facilitate the delivery of a vehicle. The vehicle may be aqueous, organic or non-organic based. The production of gas may be from a suitable electrolytic material (US 5354264) or galvanic cell (US 5242565) and is controlled by suitable circuitry.

The device of Figure 5 shows improvements to enable a more controlled delivery of vehicle to a body cavity. The addition of a tube **9** (or indeed any passageway from one end to the other) facilitates the maintenance of a constant pressure within the cavity **10** in relation to the exterior pressure **8**.

Example 1:

Formulation: Progesterone 15 mg/ml dissolved in ethanol.

Device: As shown in Figure 1A

Comment: Delivery profile characterised by a dose dump soon after insertion, followed by a reduction in plasma progesterone delivery on day due to the dose dump. See Figure 6. Figure 6 shows a plot of plasma progesterone concentration following the intra vaginal insertion of a device as per Figure 1A. Error bars are standard error means.

Example 2:

Formulation 1: Progesterone 15 mg/ml dissolved in ethanol.

Formulation 2: Progesterone 15 mg/ml suspended in water.

Formulation 3: Progesterone 15 mg/ml dissolved in hydroxypropyl b-cyclodextrin (20%w/v) solution.

Device: As shown in Figure 1B.

Comment: Delivery profile characterised by a rapid rise to desired levels soon after insertion, followed by a controlled delivery of progesterone over the remained of the insertion period. See Figure 7. Figure 7 shows a plot of the plasma progesterone concentration following the intra vaginal insertion of a device as per Figure 1B containing 1 of 3 formulations; alcoholic solution (diamond symbol), aqueous

suspension (triangle symbol with broken line) or aqueous cyclodextrin (square symbol). Error bars are standard error means.

Figures 8A to 8D and Figures 9A to 9D describe options available for circuits where respectively (Figures 8A to 8D) and electrolytic cell and (Figures 9A to 9D) a battery or gas cell of the type described by US Patent 5,242,565 is used. Appropriate electrolytic cell is that using, for example, a hydrogel as disclosed in US Patent 5,354,264.

The present invention as can be seen from the disclosure and the drawings (including those of the prior art referenced earlier in respect of vaginal tract retention features) can be used to deliver progesterone requirements prior to active withdrawal to allow the onset of oestrus. Again reference is drawn to such art as to insertion, retention options and withdrawal facilitating options.

CLAIMS:

1. **A liquid delivery device** suitable for liquid delivery in a body cavity when inserted therein, said comprising or including

a housing defining a barrel with an outlet,

a piston disposed in said barrel and moveable to reduce the available volume for liquid between said piston and said outlet,

a liquid within said barrel between said outlet and said piston, and

a battery powered electrical circuit disposed in said housing capable of being energised to generate gas or gases confined within said housing yet capable of moving said piston along said barrel thereby to express liquid out through said outlet.

2. A device as claimed in claim 1 wherein the battery itself of said electrical circuit emits said gas or gases upon energisation of the electrical circuit by said battery.

3. A device as claimed in claim 1 wherein said electrical circuit defines an electrolysis cell with a hydrogel or electrolyte and the gas issues or gases issue from said hydrogel or electrolyte.

4. A device as claimed in claim 2 wherein the battery powered electrical circuit includes a battery of a kind as disclosed in US Patent 5,242,565.

5. A device as claimed in claim 3 wherein said battery powered electrical circuit includes an electrolysis cell of a kind as disclosed in US Patent 5,352,464.

6. A device of any one of the preceding claims wherein said electrical circuit provides a continuous rate of gas production by the action of a continuous current to the electrolysis cell or gas emitting battery.

7. A device of any one of claims 1 to 5 wherein said electrical circuit provides a discontinuous rate of gas production by the action of a discontinuous current, as provided by a microprocessor, to the electrolysis cell or gas emitting battery.

8. A device of claim 6 wherein said battery powered electrical circuit provides a continuous rate of gas production dependent upon at least one of the group consisting of

(a) a selected resistor in series,

(b) a selected variable resistor and a setting of a desired resistance in series, and

(c) a selected microprocessor to control the current.

9. A device as claimed in claim 7 wherein said battery powered electrical circuit includes a selected microprocessor to control the current to the electrolysis cell or gas emitting cell.

10. A device as claimed in any one of the preceding claims wherein the battery powered electrical circuit is one having a known or calibrated profile of gas generation that will lead to a related profile of liquid release from said outlet.

11. A device as claimed in any one of the preceding claims which is an intra vaginal device.

12. A device as claimed in claim 11 wherein said housing has associated therewith at least one deployable retention member to enable the retention of the device in the vagina after insertion in the vagina of a target mammal whilst said at least one retention member is not deployable.

13. A device as claimed in claim 12 wherein said at least one retention member comprises at least two wings which resiliently deploy once inserted.

14. A device as claimed in any one of the preceding claims wherein said liquid includes progesterone in an appropriate liquid carrier.

15. A device as claimed in any one of claims 1 to 10 which is an intra ruminal device.

16. A device as claimed in claim 15 wherein said intra ruminal device is retainable in the rumen of a target mammal by means of its density at least up until the depletion of the liquid from said housing or by deployment of at least one retention member.

17. A device as claimed in any one of the preceding claims wherein said liquid includes at least one or more of water, ethanol and benzyl alcohol.

18. A device as claimed in any one of the preceding claims wherein said battery powered electrical circuit includes a switch capable of being actuated to immediately or after a delay commence the generation of a gas or gases.

19. A device as claimed in any one of the preceding claims wherein said outlet is provided with a closure capable of being removed, ruptured or dissolved in body fluids.

20. A device as claimed in claim 19 wherein said closure is capable of being removed or ruptured under the pressurisation of the liquid within said housing upon

energisation of the battery powered electrical circuit.

21. A device as claimed in any one of the preceding claims wherein said liquid is of a volume of from 5 to 100 mL and said piston is movable within said housing to express substantially all of such liquid from the housing.

22. A device of any one of the preceding claims insertable, retainable and removal from the vaginal tract of a target species mammal, there being a conduit or passageway disposed to allow pressure equalisation outside of the device at the innermost and outmost extent of the device in the vaginal tract.

23. A device as claimed in any one of the preceding claims substantially as hereinbefore described with reference to the accompanying drawings.

24. **An intra vaginal delivery device** comprising or including

a housing defining a barrel with an outlet,

variable geometry vaginal retention means carried by said housing,

a piston disposed in said barrel and moveable to reduce the available volume for liquid between said piston and said outlet,

a progesterone carrying liquid within said barrel between said outlet and said piston, and

a battery powered electrical circuit disposed in said housing capable of being energised to generate gas or gases from the battery of said battery powered electrical circuit, such generated gas or gases being confined within said housing and being capable of moving said piston along said barrel thereby to express liquid out through said outlet

and wherein said battery powered electrical circuit provides a discontinuous or continuous gas production upon initiation of energisation with rate and/or timing dependent upon at least one of the group consisting of

(a) a selected resistor in series,

(b) a selected variable resistor and a setting of a desired resistance in series, and

(c) a selected microprocessor to control the current.

25. **An intra vaginal delivery device for a target species mammal** comprising or including

an elongate housing defining a barrel with an outlet at one end (the "outlet end")

a piston disposed in said barrel and moveable towards the outlet end to reduce the available volume for liquid between said piston and said outlet,

a progesterone including liquid within said barrel between said outlet and said piston, the volume of such liquid being from 5 to 100 mL,

wings dependent from said housing capable of self deployment from a vaginal tract insertion condition to assume a vaginal tract retention geometry for the target species mammal,

a battery powered electrical circuit disposed in said housing at the non outlet end region thereof capable of being initialised in order to energise the electrical circuit from the battery thereof, such battery generating once the electrical circuit is energised at least one gas confined within said housing, such gas being capable when in sufficient quantities to move said piston along said barrel thereby to express said liquid out through said outlet.

26. **A method of providing an active release of a liquid within a body cavity of a target species mammal** which comprises or includes

locating in such a body cavity a device as claimed in any one of the preceding claims with said battery powered electrical circuit energised or committed to be energised.

27. **A method of delivering an active amount of a progesterone into the vaginal tract of a target species mammal** which comprises or includes

locating a device as claimed in any one of claims 1 to 25 in such tract after initiation of the device, and

allowing the device to actively express the liquid from said housing under the effect, via said piston, of the gas or gases generated by the energised battery powered electrical circuit.

28. A method as claimed in claim 27 wherein said method involves removing said device after a sufficient time of liquid delivery.

29. A method of providing delayed release of a liquid vehicle into a body cavity of a mammal or into a liquid environment which comprises or includes the operative use of a device of any one of claims 1 to 25.

30. A method as claimed in any one of claims 26 to 29 when performed substantially as hereinbefore described with or without reference to any one or more of the accompanying drawings.

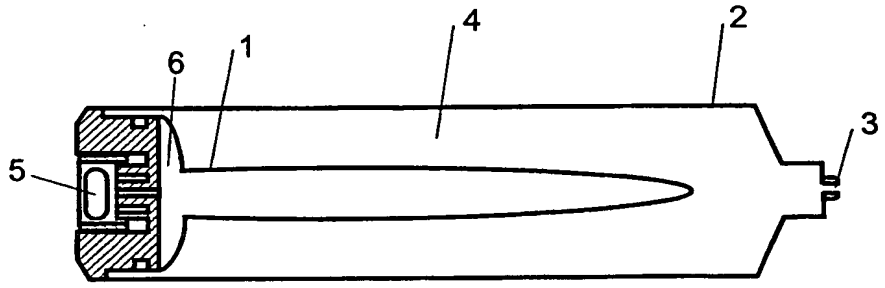


FIGURE 1A

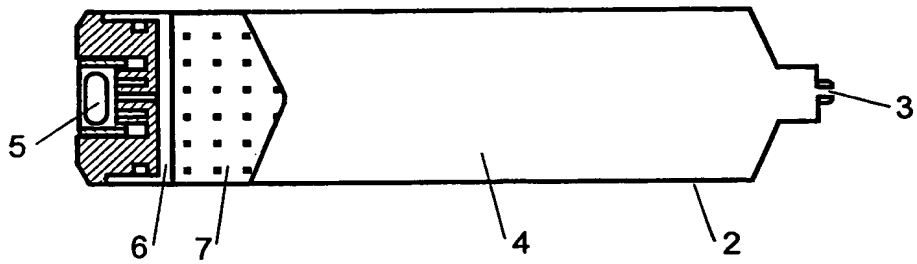


FIGURE 1B

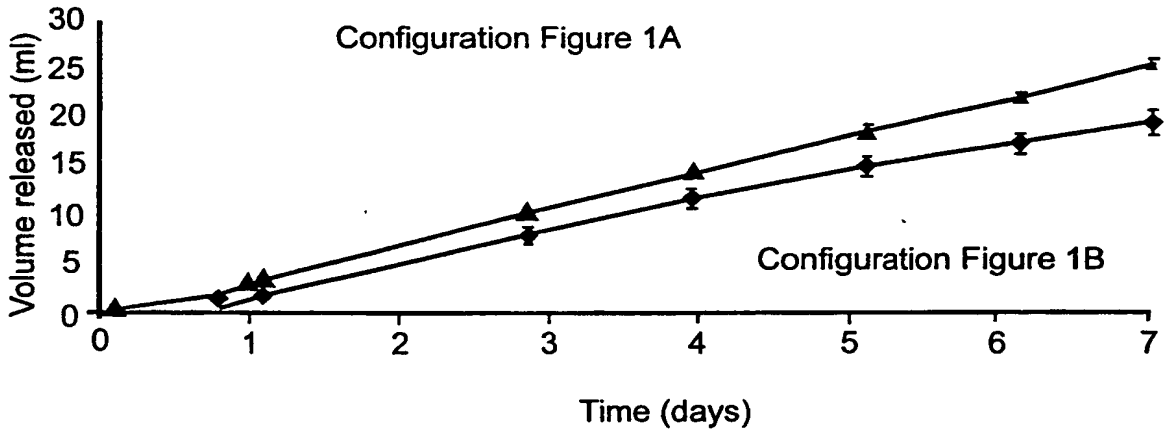

Configuration Figure 1A
Configuration Figure 1B
Volume released (ml)
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
Time (days)

FIGURE 2

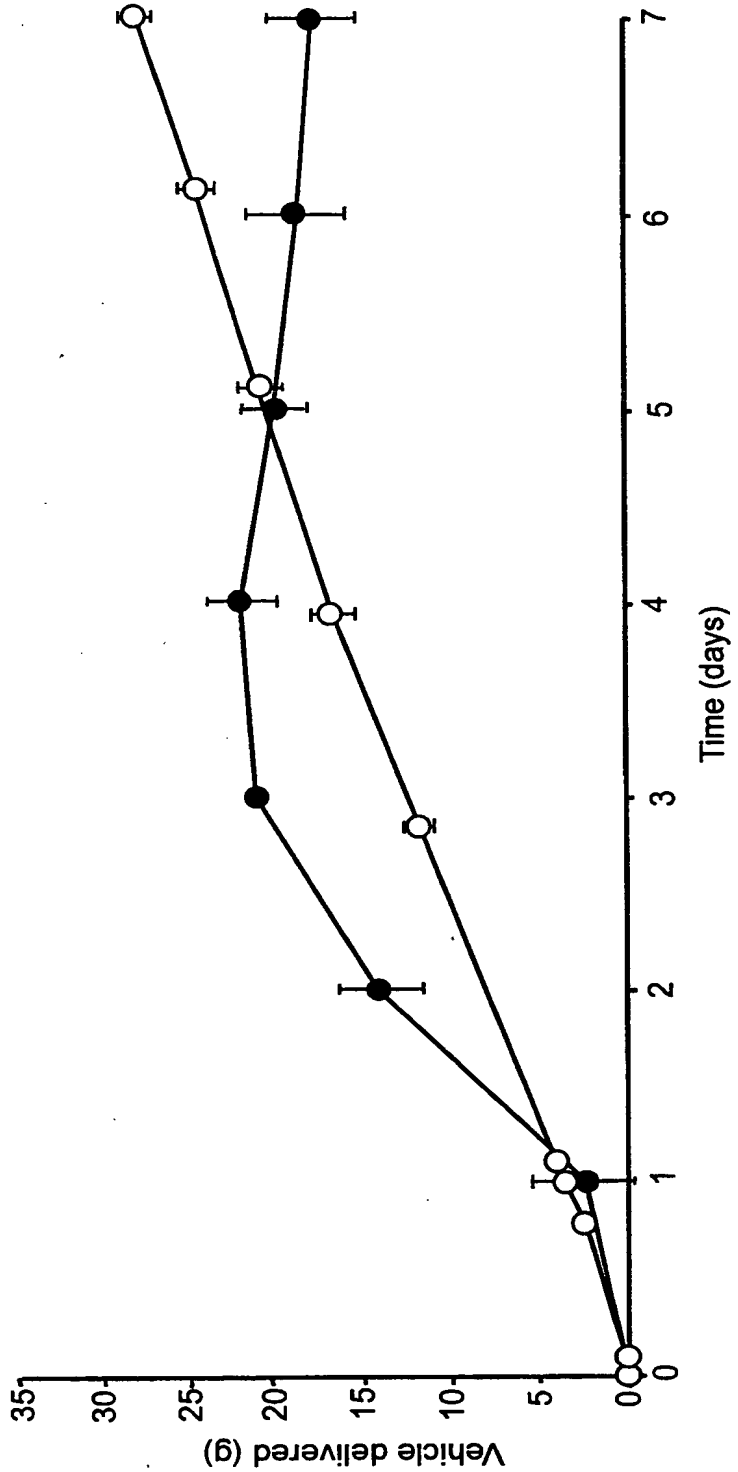


FIGURE 3

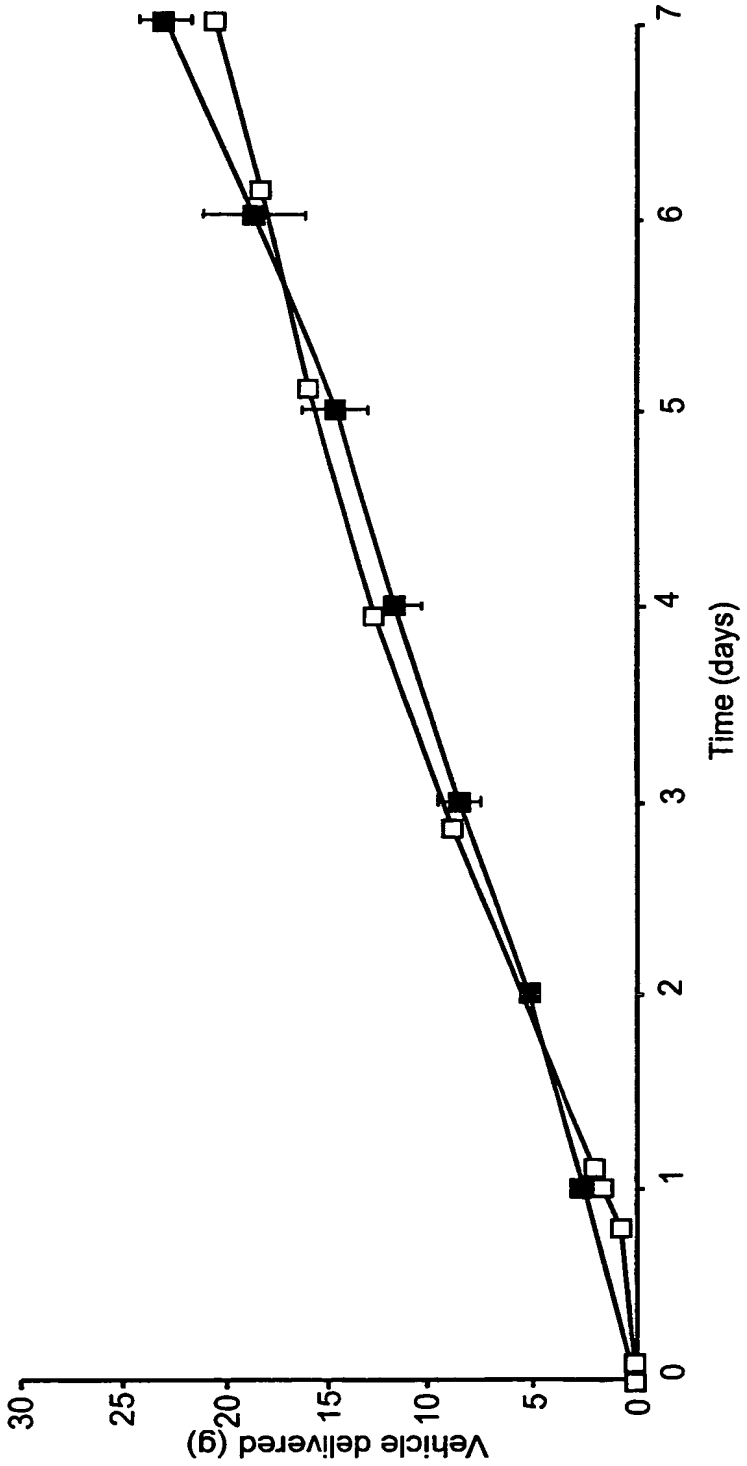


FIGURE 4

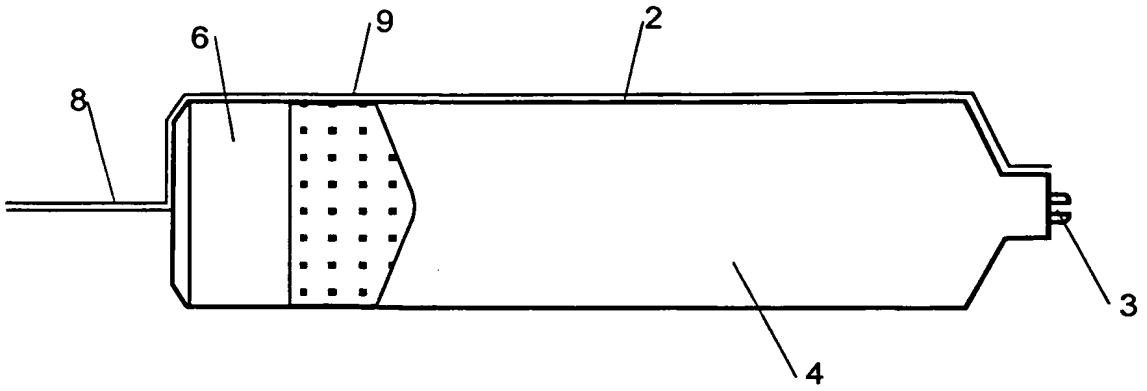


FIGURE 5

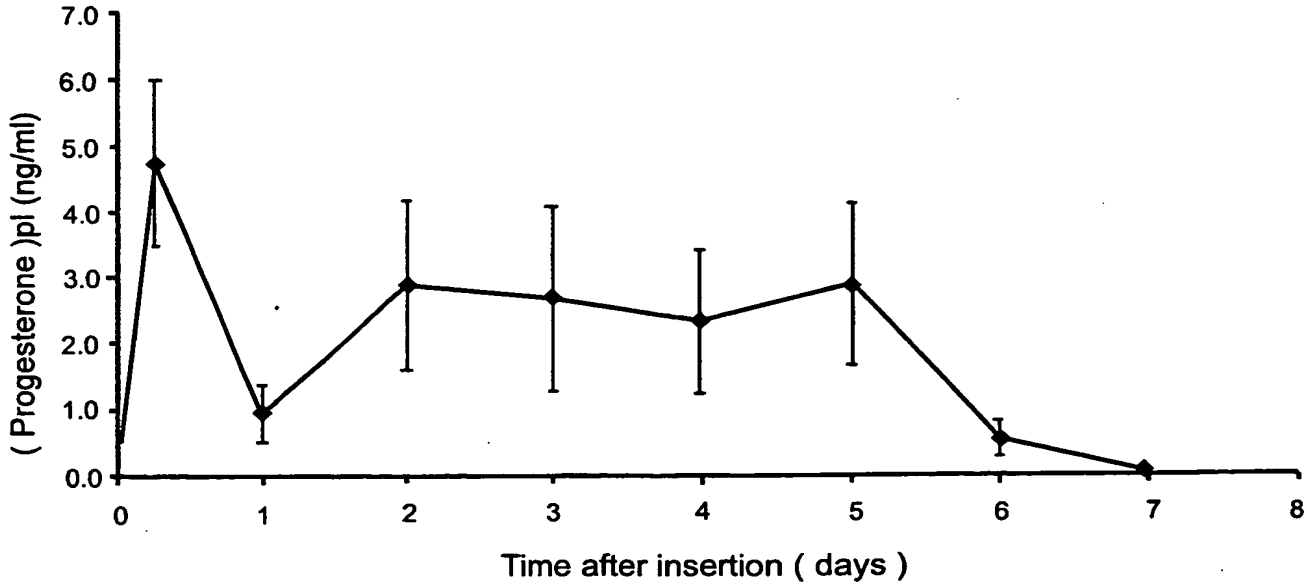


FIGURE 6

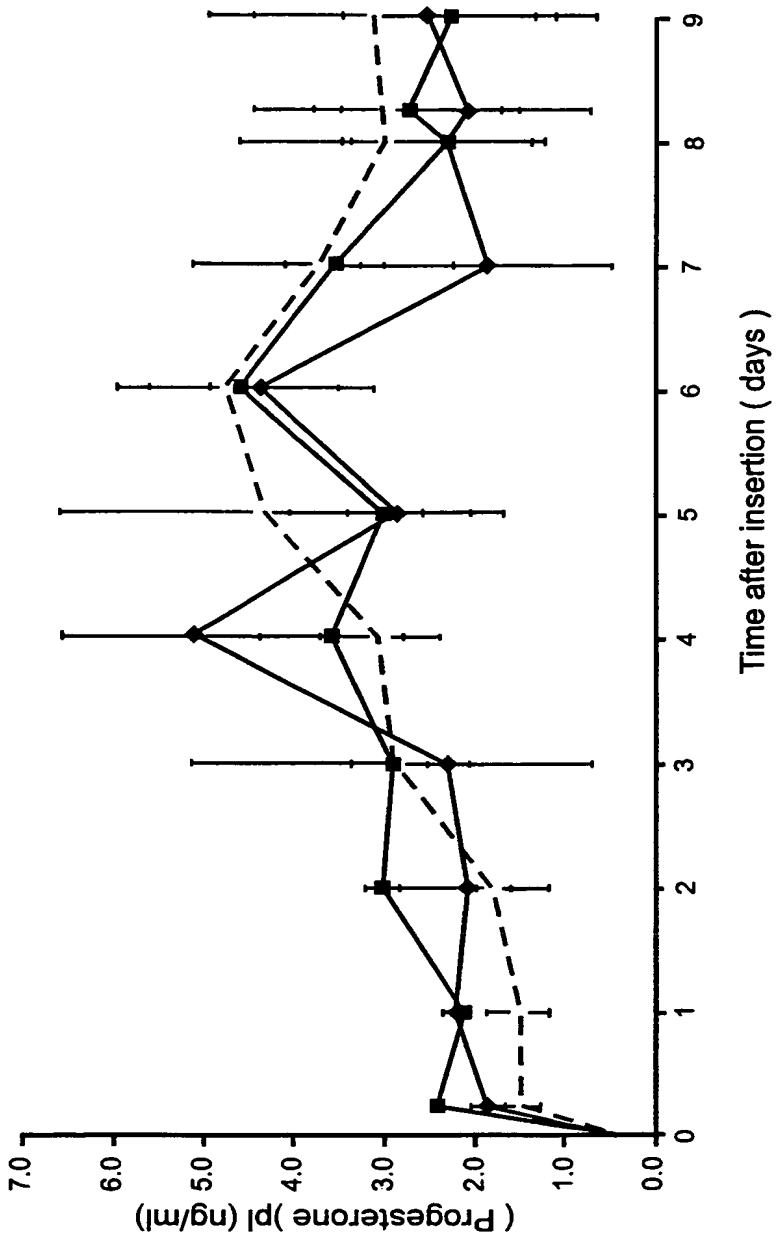

(Progesterone)pl (ng/ml)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
0
1
2
3
4
5
6
7
8
9
Time after insertion (days)

FIGURE 7

FIGURE 8A

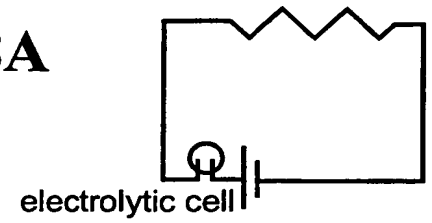


FIGURE 8B

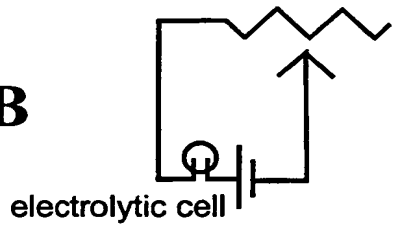


FIGURE 8C

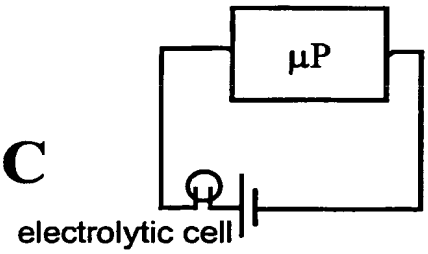


FIGURE 8D

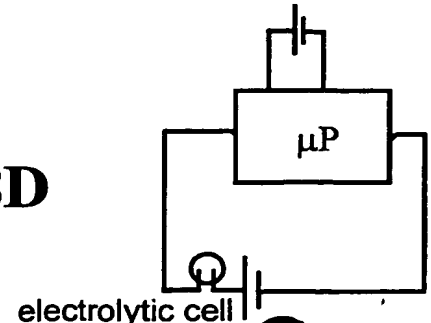


FIGURE 9A

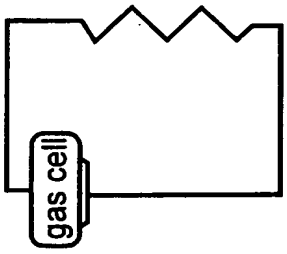


FIGURE 9B

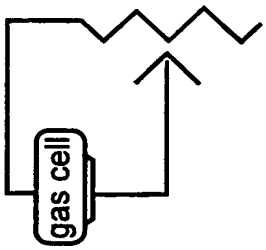


FIGURE 9C

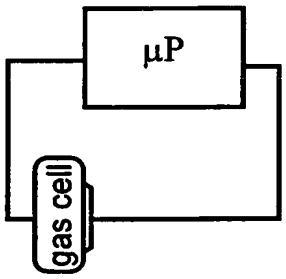
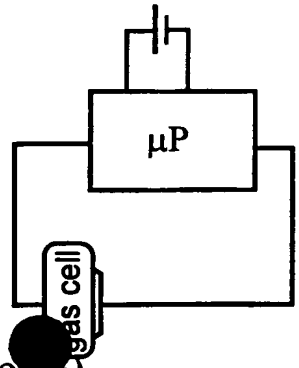


FIGURE 9D



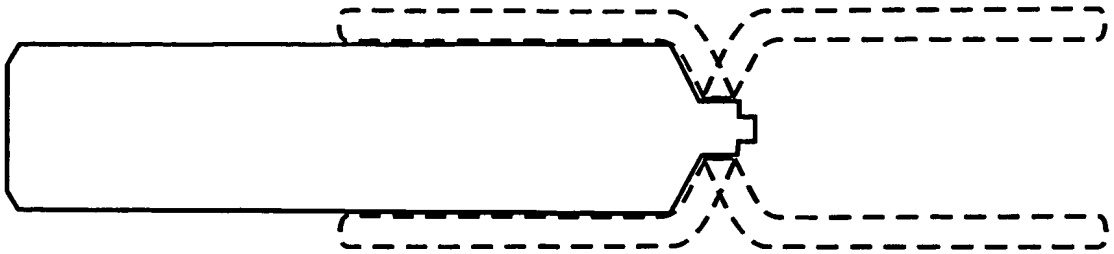


FIGURE 10A

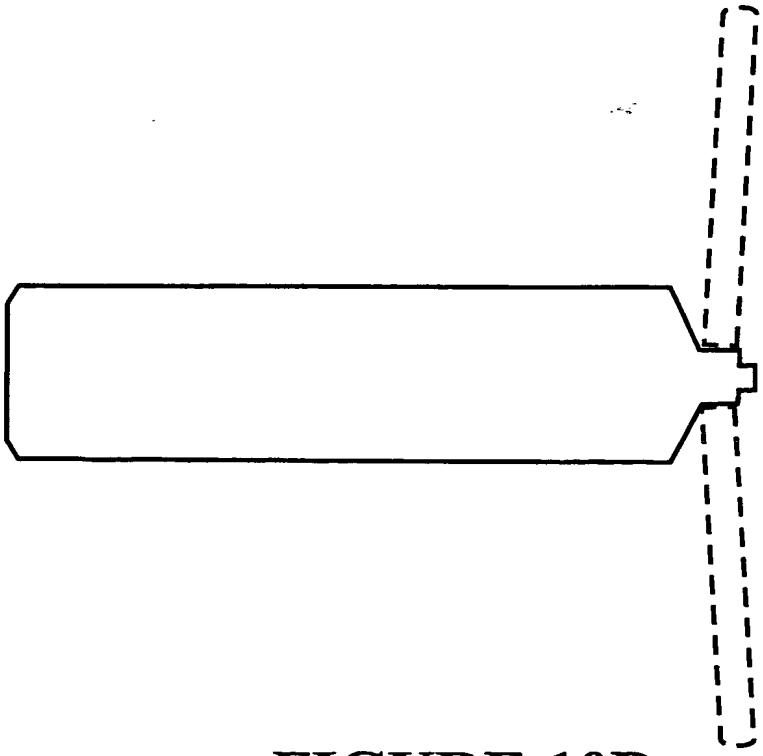


FIGURE 10B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00093

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61D 7/00, A61M 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61D, A61 M, A61J, A61K, A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent: piston, plunger, gas, oxygen, hydrogen, battery, electrolyte

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/33452 A1 (DEC INTERNATIONAL NZ LIMITED) 6 August 1998 entire document	1, 3, 6, 8, 10-15, 17-19, 21, 24-28
Y		9, 18, 19
X	US 5242565 A (WINSEL) 7 September 1993 Figure 10, column 14 line 67 – column 15 line 13	1-3, 6, 8, 10, 14, 17-19, 21
X	WO 99/07346 A1 (CERAMATEC, INC.) 18 February 1999 entire document	1, 3, 6, 8, 10-15, 17-19, 21, 26-28

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2000	19 SEP 2000
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **STEVEN WEISS** Telephone No : (02) 6283 2466

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00093

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/01165 A1 (ELAN MEDICAL TECHNOLOGIES LIMITED) 20 January 1994 entire document	1, 3, 6, 10, 18, 19, 26
Y	figures 1-7, page 4 line 19, page 7, lines 25-28	18, 19
Y	WO 96/29025 A1 (ADVANCED ANIMAL TECHNOLOGY LIMITED) 26 September 1996 abstract	9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00093

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos : **4, 5, 23, 30**

because they relate to subject matter not required to be searched by this Authority, namely:

Under PCT Rule 6.2(a), Claims 4 and 5 relate to subject matter not described within the specification.
Under PCT Rule 6.2(a), Claims 23 and 30 relate to subject matter disclosed in the drawings.

2. [ ] Claims Nos :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ00/00093

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9833452	AU	57838/98	NZ	314175	ZA	9800805
US	5242565	AU	70321/87	CA	1333579	DE	3643352
		EP	343157	JP	6000190	WO	8804750
WO	9907346	AU	88989/98	US	5951538		
WO	9401165	AU	45123/93	US	5318557	DE	69315579
		EP	651667	NZ	253782	ZA	9304956
WO	9629025	AU	51274/96	CA	2216256	EP	820258
		EP	988838	EP	990425		

END OF ANNEX

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CALHOUN, Douglas, C.
A J Park
6th floor, Huddart Parker Building
Post Office Square
P.O. Box 949
Wellington 6015
NOUVELLE-ZÉLANDE

Date of mailing (day/month/year) 30 August 2001 (30.08.01)	
Applicant's or agent's file reference P427472 DJJ	IMPORTANT NOTIFICATION
International application No. PCT/NZ00/00093	International filing date (day/month/year) 09 June 2000 (09.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
DEC RESEARCH 558 Te Rapa Road Hamilton New Zealand	NZ	NZ
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
INTERAG 558 Te Rapa Road Hamilton New Zealand	NZ	NZ
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Gabriele BAEHR
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004282358

PCT NT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

CALHOUN, Douglas, C.
A J Park
6th floor, Huddart Parker Building
Post Office Square
P.O. Box 949
Wellington 6015
NOUVELLE-ZÉLANDE

Date of mailing (day/month/year)
30 August 2001 (30.08.01)

Applicant's or agent's file reference
P427472 DJJ

IMPORTANT NOTIFICATION

International application No.
PCT/NZ00/00093

International filing date (day/month/year)
09 June 2000 (09.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
DEC RESEARCH
558 Te Rapa Road
Hamilton
New Zealand

State of Nationality: NZ
State of Residence: NZ
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
INTERAG
558 Te Rapa Road
Hamilton
New Zealand

State of Nationality: NZ
State of Residence: NZ
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Gabriele BAEHR

Telephone No.: (41-22) 338.83.38